REMARKS

Request for Continued Examination

The present submission is a Request for Continued Examination (RCE) under 37 CFR §1.114(b), of U.S. Patent Application Serial No. 10/659,684. The Notice of Appeal for the above-named application was filed on March 5, 2008.

Claims 1-3, 5, 6, and 9-11 are pending. Claims 9-11 have been amended. Claims 4 and 7 are being canceled. Claim 8 was previously canceled. Claims 12-47 have been canceled because they are in non-elected restriction groups. Applicants expressly reserve the right to prosecute the canceled subject matter in other related applications.

Rejections from Office Action dated September 5, 2007

Reconsideration and withdrawal of the rejections in view of the above amendments and following remarks are respectfully requested. Claims 4, 7, 8 and 12-47 having been canceled, the pending claims of the instant application are claims 1-3, 5, 6, and 9-11.

Claims 9 and 10 are amended to correct inadvertent typographical errors. Claim 11 has been amended to removed the phrase "a polypeptide" as it is redundant based on the definition provided in the instant specification. The Office Action dated September 5, 2007, on page 4, states a generic definition for a peptide as less than ten amino acids, and thereby acknowledges that amino acid residues 32-162, i.e. 130 residues, would fall within the definition of a polypeptide. Applicants believe that the amendment merely makes the claim less verbose, but does not alter the scope in any way.

Rejections Under 35 U.S.C. §112

Enablement

The Examiner rejected claims 1-7 and 9-11 under 35 U.S.C. §112, first paragraph alleging that the specification, while being enabling for certain polypeptides of SEQ ID NO:2, allegedly does not reasonably provide enablement for all possible variants contemplated by the applicant, including those at are at least 90% or 95% identical to fragments of SEQ ID NO: 2 . The claims also recite the phrase "a polypeptide" and thus, are broadly interpreted by the Examiner as reading upon: (i) protein variants with any

number of deletions, substitutions, or additions and (ii) fragments of SEQ ID NO:2, including sequences only 6 amino acids in length .

Applicants respectfully traverse the rejections. First, applicants will address the part of the rejection focused on the phrase "a polypeptide." At the time this Office Action was issued, it was the Office's practice to interpret phrases such as "a polypeptide" or "a sequence of amino acids" as reading on any and all fragments and variants encompassed by the polypeptide or sequence of amino acids being claimed ostensibly without regard to the context in which phrase was used in the claim. However, applicants believe since then the blanket rejection given whenever the term "a" was identified in a claim has evolved in the Office to respect the context with which it is used. Now when the context of "a polypeptide" (or "a sequence of amino acids") in a claim is clearly and plainly limited to those enabled, then amendment is not required.

In this case, applicants assert that claims 1-3, 5, 6, and 9-11 do not have to be amended to remove the phrase "a polypeptide" because the context of the claim language in these claims is such that only a specified amount of variation is permitted, not the unlimited variation previously asserted by the Office. For example, in claim 1, the polypeptide must comprise an amino acid sequence that is at least 90% identical to the sequence from amino acid 41 to amino acid 148 of SEQ ID NO: 2. Any variation within the polypeptide must be limited to modifications that retain at least 90% identity to a defined region, i.e., from amino acid residues 41 to 148 of SEQ ID NO: 2. This language clearly and plainly does not permit ten amino acid fragments, or unlimited variations. Likewise, claim 2 is further limited to modifications that are at least 95% identical to the sequence from amino acid 41 to amino acid 148 of SEQ ID NO: 2, and claim 3 cannot have any modifications. When "a polypeptide" is construed in the proper context, it is defined as a sequence of amino acid residues (e.g. 41-148 or 31-162) with limitations on the percent of modification clearly identified in the claim, and the claims do not read on any and all (i) protein variants with any number of deletions, substitutions, or additions and (ii) fragments of SEQ ID NO:2, including sequences only 6 or 10 amino acids in length. Thus, claims reasonably correlate to the scope of the enablement provided. Consequently, applicants assert that the claims are enabled as written.

Regarding claim 11, the claim incorporates the phrase "a polypeptide comprising amino acid residues...". This particular context within a claim, where the phrase "a polypeptide" is followed by "comprising", has been recently reconsidered by the Office, and now such claims must be interpreted to literally cover a polypeptide that includes the complete sequence of amino acids from residue 32 to residue 162. Therefore, applicants would request this rejection also be withdrawn.

Second, the Examiner also maintained that while the specification discloses the biological function of the zalpha11 ligand (aka IL-21), applicants have not provided a correlation between the variants and the biological functions disclosed. It is the Examiner's belief that in the absence of such correlation, further guidance is required or undue experimentation would be required by one skilled in the art. Applicants maintain the claimed polypeptides are enabled and the Office is incorrect because (1) the interpretation is broader than is reasonable and (2) guidance for those skilled in art is provided in the specification for the claimed polypeptides.

The first aspect of applicants' argument is discussed in detail above, but applicants would point out that support for such a broad interpretation as the Office is using is not found in the application, for the simple reason that applicants never intended to make such a claim and therefore never described or enabled DNA encoding any and all amino acid sequences that were 2 or 10 amino acid residues long.

With regard to the second aspect, applicants assert the specification does provide the guidance necessary for one skilled in the art to do any routine experimentation necessary to identify which polypeptides fall within the scope of the claims. Through the use of alignments of the previously-known cytokines related to zalpha11 ligand (Table 1) and the newly discovered human and mouse species of zalpha11 provided (SEQ ID NOS: 2 and 56, respectively), the specification describes structural and functional relationships within the cytokine family, and the present inventors establish the requisite guidance necessary for one skilled in the art to make and use claimed variants. As was previously stated in the Response to the Office Action dated June 18, 2007, applicants describe the protein family in detail; defining helices A-D and loop structures. For example, on pages 10-11 the specification discloses:

> In general, cytokines are predicted to have a four-alpha helix structure, with helices A, C and D being most important in ligand-receptor interactions, and are more highly conserved among members of the family. Referring to the human zalpha11 Ligand amino acid sequence shown in SEQ ID NO:2, alignment of human zalpha11 Ligand, human IL-15, human IL-4, and human GM-CSF amino acid sequences it is predicted that zalpha11 Ligand helix A is defined by amino acid residues 41-56; helix B by amino acid residues 69-84; helix C by amino acid residues 92-105; and helix D by amino acid residues 135-148; as shown in SEQ ID NO: 2. Structural analysis suggests that the A/B loop is long, the B/C loop is short and the C/D loop is parallel long. This loop structure results in an up-up-down-down helical organization. The cysteine residues are absolutely conserved between zalpha11 Ligand and IL-15, as shown in Figure 1. The cysteine residues that are conserved between IL-15 and zalpha11 Ligand correspond to amino acid residues 71, 78, 122 and 125 of SEQ ID NO: 2. Conservation of some of the cysteine residues is also found in IL-2, IL-4, GM-CSF and zalpha11 Ligand corresponding to amino acid residues 78 and 125 of SEQ ID NO: 2, as shown in Figure 1. Consistent cysteine placement is further confirmation of the four-helical-bundle structure. Also highly conserved in the family comprising IL-15, IL-2, IL-4, GM-CSF and zalpha11 Ligand is the Glu-Phe-Leu sequence as shown in SEQ ID NO: 2 at residues 136-138, as in Figure 1.

Not only does the specification describe and enable genera of variants, but species are described and enabled as well. The specification teaches which amino acids can vary from SEQ ID NO: 2 as much as 10%, and still result in a protein that is biologically functional, e.g. binds the zalpha11 receptor of SEQ ID NO:115.

As previously explained, the specification discloses at page 12:

> While helix A is relatively well-conserved between human and murine zalpha11 Ligand, helix C is more divergent. While both species have predominant acidic amino acids in this region, the differences may account for species specificity in interaction between zalpha11 Ligand and its "beta" type receptor, zalpha11. Loop A/B and helix B of zalpha11 Ligand are well-conserved between species; although no receptor subunit corresponding to IL-2Rα has yet been identified, conservation through this region suggests that it is functionally significant. The D helices of human and murine zalpha11 Ligand are also highly

> conserved. Zalpha11 receptor antagonists may be designed through mutations within zalpha11 Ligand helix D. These may include truncation of the protein from residue Gln_{145} (SEQ ID NO: 2), or mutations of Gln_{145} or Ile_{148} (of SEQ ID NO: 2; corresponding to Tyr_{124} in human IL-4) to residues such as Ala or Asp. Any mutation which disrupts the zalpha11 Ligand helical structure may abolish binding with its receptor and thus inhibit signaling.

Thus, the specification provides the skilled artisian with all the tools needed to make routine any experimentation necessary to demonstrate that a claimed polypeptide falls within the scope of the instant claims.

Moreover, it is not surprising that others using the disclosures and teachings in the instant specification have identified polypeptides comprising amino acid residues at least 90% identical to residues 41 (Gln) to 148 (Ile) as shown in SEQ ID NO:2 and that these polypeptides have the same activities as the presently claimed inventions, i.e. bind the cognate receptor and cause proliferation in an NK cell assay. It is well accepted that an applicant can use post-filing publications as evidence of the level of skill in the art at the time the application was filed (MPEP 2164.05), and that enablement is supported.

Applicants teachings combined with that which was known and available to those skilled in the art has resulted in publication of variants polypeptides that not only fall within the scope of the claimed invention but could be predicted using the guidance provided by the specification. For example, in December 2004, Cunningham et al., (PCT/US2004/018903 (published as WO 2004/112703)) describes several variant IL-21 polypeptides with 11 to 14 amino acid residue changes in the sequence between residues 32 and 162 of SEQ ID NO:2. Cunningham et al. used the polynucleotide and polypeptide sequences discovered and provided by present the inventors as the bases for their studies. Over a range of 131 amino acids, the percent identity between the variant and reference SEQ ID NO:2 is between ~89-92%. By comparing Figure 2 of Cunningham et al. to, for example, page 34 of the instant specification, one can see the changes made are either conservative or avoid the regions applicants' teach are important for activity. Analyses were performed using programs and assays described or similar to those described in the

instant specification; many of which have been known to those in the art for years using commercially available reagents. Cunningham et al. provides evidence that applicants' specification provided an enabling disclosure for claims to an isolated polypeptide comprising a sequence of amino acid residues that is at least 90% identical to residues 41 (Gln) to 148 (Ile) as shown in SEQ ID NO:2 and an isolated polypeptide comprising a sequence of amino acid residues that is at least 90% identical to residues 32 (Gln) to 148 (Ile) as shown in SEQ ID NO:2.

The distinctive use of "a polypeptide comprising a sequence of amino acid residues that is at least 90% identical to residues 32 (Gln) to 162 (Ser) as shown in SEQ ID NO:2" limits the modifications and variations that can be to any polypeptide that would fall within the scope of the claims, and these polypeptides are enabled by the instant specification. Thus, applicants assert that the claims are enabled and fully described and respectfully request the rejection be withdrawn.

Written Description

The Examiner also rejected claims 1-7 and 9-11 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants respectfully traverse the rejection and maintain that the claims meet the written description requirements. Possession of an isolated polypeptide comprising a sequence of amino acid residues that is at least 90% identical to residues 41 (Gln) to 148 (Ile) as shown in SEQ ID NO:2 only requires the disclosure of SEQ ID NO:2 combined with the pre-existing knowledge in the art regarding the genetic code and its redundancies, as stated in the **Written Description Training Materials, Example 11: Percent Identity**, published March 25, 2008. The instant specification provides said zalpha11 Ligand sequences (i.e. SEQ ID NOS: 2 and 56), with a discussion of the state of the art referred to in the Written Description Training Materials, for one example, on pages 13-16.

In addition, the instant specification provides more. It discloses both human and mouse zalpha11 Ligand sequences (SEQ ID NOS:1 and 2 for human and SEQ ID NOS: 55 and 56 for mouse), with guidance as to what structural elements are conserved; both within the family and between ligands that bind a common receptor subunit. Such teachings provide evidence that applicants were in possession and could recognize polypeptides that are within the genus of the claimed polypeptides. Moreover, the specification teaches structure and function correlations as described above.

Applicants respectfully submit that the written description requirement for claims 1-3, 5, 6, and 9-11 under 35 U.S.C. § 112, 1st paragraph has been met. The level of skill and knowledge in the art would allow the skilled artisian to identify all claimed isolated polypeptides and pharmaceutical compositions comprising a sequence of amino acid residues that are at least 90% identical to residues 41 (Gln) to 148 (Ile) as shown in SEQ ID NO:2; or at least 95% identical to residues 41 (Gln) to 148 (Ile) as shown in SEQ ID NO:2; or at least 90% identical to residues 32 (Gln) to 148 (Ile) as shown in SEQ ID NO:2; or at least 95% identical to residues 32 (Gln) to 162 (Ser) as shown in SEQ ID NO:2; or that is identical to residues 41 (Gln) to 148 (Ile) as shown in SEQ ID NO:2, when combined with the disclosure of these sequences. The specification also discloses two species of zalpha11 Ligand, regions of conservation, and critical binding residues. One skilled in the art would recognize that the applicants were in possession of the claimed invention as a whole at the time of filing, and therefore, applicants request the rejection be withdrawn and the claims allowed.

Conclusion

In light of the above amendments and remarks, reconsideration and withdrawal of the rejections are respectfully requested. It is, thus, respectfully requested that claims 1-3, 5, 6, and 9-11 are in condition for allowance and notification to that effect is respectfully requested. If for any reason the Examiner feels that a telephone conference would expedite prosecution of the application, the Examiner is invited to telephone the undersigned at (206) 442-6672.

Respectfully Submitted,

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